REMARKS

In view of the following remarks, the Examiner is requested to allow Claims 21-34 and 42-44, the only claims pending and currently under examination.

Formal Matters

Claim 42 is amended to clarify that the extension product remains hybridized to the single stranded template nucleic acid. Exemplary support for this amendment is found throughout the specification, for example, at page 5, lines 2-5, page 14, lines 7-9, etc. Claim 43 is amended to recite that the primer nucleic acid is extended by a singe complementary nucleotide using a polymerase in the presence of four distinguishable nucleotides each labeled with a 3' cleavable tag. Exemplary support for this amendment is found throughout the specification, for example, at page 5, lines 2-12. New claim 44 recites repeating steps (b) to (d) on the extension product produced in step (c) of claim 43. Exemplary support for this claim is found throughout the specification, for example, at page 6, lines 13-15, page 19, lines 17-21, etc.

Claim Rejections under 35 U.S.C. § 102

Claims 21-28, 31, 33-34, and 42-43 are rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Schmidt (WO 99/02728).

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. *Verdegaal Bros. v. Union Oil of California*, 814 F.2d 628, 631, (Fed. Cir. 1987).

The standard for anticipation under section 102 is one of strict identity. An anticipation rejection requires a showing that each limitation of a claim be found in a single reference, *Atlas Powder Co. v. E.I. DuPont de Nemours & Co.,* 224 U.S.P.Q. 409, 411 (Fed. Cir. 1984). Further, an anticipatory reference must be enabling, see *Akzo N.V. v. United States Int'l Trade Comm'n* 808 F.2d 1471, 1479, 1 U.S.P.Q.2d 1241, 1245 (Fed. Cir. 1986), *cert denied*, 482 U.S. 909 (1987), so as to place one of ordinary skill in possession of the claimed invention. To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.* 334 U.S. P.Q.2d 1565 (Fed. Cir. 1995).

Claim 21 recites a method of determining a nucleic acid sequence that includes: (a) hybridizing a primer nucleic acid to a single stranded template nucleic acid; (b) extending the

primer nucleic acid by at least one complementary nucleotide to produce an extension product that includes a 3' cleavable tag, wherein the at least one complementary nucleotide includes a 3' cleavable tag; (c) cleaving the 3' cleavable tag from the extension product to produce a cleaved tag, not bound to the at least one complementary nucleotide, and an extension product that includes the at least one complementary nucleotide hybridized to the template nucleic acid sequence; and (d) detecting the cleaved tag away from the extension product to determine the nucleic acid sequence.

Accordingly, claim 21 requires, *inter alia*, that the extension product and the single stranded template nucleic acid remain hybridized when the 3' cleavable tag added to the extension product is cleaved.

Claim 42 recites a method of determining a nucleic acid sequence that includes: (a) hybridizing a primer nucleic acid to a single stranded template nucleic acid; (b) extending the primer nucleic acid by at least one complementary nucleotide to produce a single extension product that includes a 3' cleavable tag, wherein the at least one complementary nucleotide includes a 3' cleavable tag; (c) cleaving the 3' cleavable tag from the single extension product to produce a cleaved tag not bound to the at least one complementary nucleotide, and an extension product that includes the at least one complementary nucleotide hybridized to the template nucleic acid sequence; (d) detecting the cleaved tag away from the extension product; (e) repeating steps (b) to (d) and thereby determining the nucleic acid sequence.

Accordingly, claim 42 requires, *inter alia*, that a single extension product that includes a 3' cleavable tag is produced and that the extension product and the single stranded template nucleic acid remain hybridized when the 3' cleavable tag added to the extension product is cleaved.

Claim 43 recites a method of determining a nucleic acid sequence that includes: (a) hybridizing a primer nucleic acid to a single stranded template nucleic acid in a sample; (b) extending the primer nucleic acid by a single complementary nucleotide to produce an extension product that includes a 3' cleavable tag, wherein the extension product is produced by a polymerase in the presence of four distinguishable nucleotides, each labeled with a distinguishable 3' cleavable tag; (c) cleaving the 3' cleavable tag from the extension product to produce a cleaved tag not bound to the at least one complementary nucleotide and an extension product not separated from the single stranded template nucleic acid; and (d) detecting the cleaved tag away from the extension product.

Accordingly, claim 43 requires that the primer nucleic acid is extended by a single complementary nucleotide using a polymerase and that the extension product is not separated from the single stranded template nucleic acid.

Schmidt does not disclose a method in which the complementary nucleic acid and the template nucleic acid remain hybridized and are not separated when the tag is cleaved. Rather, Schmidt's method is one in which the complementary nucleic acid is separated from the template nucleic acid prior to cleavage. Moreover, Schmidt does not disclose a method in which a single extension product that includes a 3' cleavable tag is produced (see claim 42). Rather, Schmidt teaches producing a plurality of extension products of different lengths. Since Schmidt's method is different to that being claimed, Schmidt cannot anticipate the claims and this rejection should be withdrawn.

In attempting to establish this rejection, the Examiner argues that Schmidt discloses a method in which "a series of DNA fragments is provided by contacting a template in the presence of DNA polymerase with a mixture of nucleotides sufficient for hybridizing to the template for forming a second strand of DNA complementary to the template. The mixture comprises a set of four probes containing all four nucleotides for hybridizing to the template in which the nucleotides of each probe comprise a modified nucleotide, which is capable of polymerizing to the second strand of DNA, but blocked to prevent further polymerization and which is cleavably attached to the mass label." The Examiner further states that "Schmidt et al. also disclose an alternative implementation to use photolysable mass labels at the 3'-OH of each 4-mer oligonucleotide. The mass-label could be attached to another part of the molecule from which it can be released independently of the uncapping reaction of the 3' terminus (see pg. 46, paragraphs 4 and 5). This inherently teaches that 3' tag is cleaved from an extension product and not bound to said at least one complementary nucleotide and an extension product that includes said at least one complementary nucleotide hybridized to said template nucleic acid sequence."

As noted above, the Examiner bases this rejection on paragraphs 4 and 5 of Schmidt. However, paragraphs 4 and 5, page 46 of Schmidt when read in context do not disclose any method in which complementary nucleic acid and template nucleic acid remain hybridized or are not separated when the 3' tag is cleaved. Rather, paragraphs 4 and 5 provide alternative methods for probing immobilized Sanger ladder which is a mixture of multiple nucleic acids of varying lengths. Thus, in the methods of both paragraphs 4 and 5, the complementary nucleic acids (i.e. the Sanger ladder nucleic acids) and template nucleic acid are separated when the 3' tag is cleaved. The Applicants' position is supported by page

46, paragraph 1 of Schmidt which provides the context for paragraphs 4 and 5 on page 46. Paragraph 1 on page 46 of Schmidt is reproduced below:

> In one embodiment one can probe the immobilised Sanger ladder with every one of the possible 256 single-stranded 4 base oligonucleotides. Each of these would carry a unique identifying label corresponding to its known, sequence of 4 bp. In the 5' to 3' format, the label could be attached to the 3' -OH effectively blocking them from further extension, or a separate blocking group can be used and the label can be attached elsewhere in the molecule.

Paragraph 4 on page 26 of Schmidt describes that the probes are labeled and blocked at the 3'-OH end by a mass label. Thus, paragraph 4 further describes a first embodiment of the 5' to 3' format above (see lines 4-6 of paragraph 1 above). Paragraph 5 on page 26 of Schmidt describes that the probes are labeled by a mass label and blocked with a phosphate group, separating the steps of cleavage of the mass label and unblocking of the 3'-OH group. Thus, paragraph 5 further describes a second embodiment of the 5' to 3' format above (see lines 6-7 of paragraph 1 above).

Thus, Schmidt discusses that the methods described in the paragraphs 4 and 5 (cited by the Examiner) are two alternative embodiments of the **method of probing the immobilized Sanger ladder**, which method requires separating the individual component fragments of the Sanger ladder. It is described throughout the disclosure of Schmidt that prior to the cleavage of the mass label, one needs to separate the Sanger ladder into its component fragment lengths. See for example, the paragraph preceding page 46 (last paragraph, page 45), reproduced below:

> The immobilised matrix can then be washed to remove any unbound oligonucleotides, a water wash would probably be sufficient to disrupt hybridisation. To determine the sequence of the 4 base oligonucleotide that ligated to each Sanger fragment, one need only analyse the label attached to the 3' end of the oligonucleotide. The labelling system for use with this invention is described in PCT/GB98/00127 in which the mass of the label identifies its carrier. Such labels can be made photolabile or cleavable by a specific chemical or biological agent. As detailed in Figure 14, cleavage of the label will release it into solution in which it can be injected into an electrospray mass spectrometer for analysis, which will determine the sequence of the oligonucleotide and furthermore, its quantity. Sample results are shown in Figure 15. Prior to cleavage of labels one needs to separate the Sanger ladder into its component fragment lengths. In a mass spectrometry system this stage can be coupled to the sample loading in a LCMS system. Separation into bands can be achieved by capillary zone electrophoresis. This will then pass through a UV spectrometer to determine the quantity of DNA in each band. Following this the sample will then pass through a photocleavage module to release the mass-labels which will then be injected into an electrospray mass spectrometer for analysis of the labels in each band.

(emphasis added)

At page 49 of Schmidt, the section entitled "Ligase Chain Reaction" states that a ladder of terminated fragments in a manner that is analogous to the Sanger sequencing reaction will be generated and the identity of the terminating 4-mers can be determined by **separating the terminated fragments by capillary electrophoresis followed directly by analysis of the cleaved mass label.** (Schmidt, page 49, last two paragraphs).

Similarly, page 16, third paragraph of Schmidt states that the method "allows one to generate a Sanger ladder of fragments" and that "[o]ne can analyse the resultant sequence ladder by capillary electrophoresis followed by direct analysis of mass labels by electrospray mass spectrometry (ESMS)". Moreover, Schmidt's Fig. 4a, shows that capillary electrophoresis precedes photocleavage of the label.

Thus, each of the different embodiments of the method described in Schmidt's disclosure, when read in context, is one in which a Sanger ladder is generated and the **complementary nucleic acids are separated from the template nucleic acid prior to cleavage**, rather than a method in which the complementary nucleic acid is hybridized to the template nucleic acid or not separated from the template nucleic acid during cleavage, as required by the rejected claims.

Therefore, Schmidt cannot anticipate the claimed subject matter because it fails to disclose every element of the rejected claims.

Furthermore, with respect to claim 42, the Applicants submit that Schmidt does not disclose "extending said primer nucleic acid by at least one complementary nucleotide to produce a **single** extension product that includes a 3' cleavable tag", as required by claim 42. Rather, as established above, similar to Sanger sequencing, Schmidt generates a plurality of extension products of differing lengths, i.e., a Sanger ladder. Thus, for this additional reason, Schmidt fails to anticipate claim 42.

Moreover, with respect to claim 43, the Applicants submit that Schmidt does not disclose extending the primer nucleic acid by a single complementary nucleotide using a polymerase to produce an extension product that includes a 3' cleavable tag, cleaving the tag to produce a cleaved tag and an extension product not separated from the template nucleic acid and detecting the cleaved tag, as required by claim 43. Rather, Schmidt generates a plurality of extension products, i.e., a Sanger ladder. Schmidt separates this extension product from the template nucleic acid by capillary electrophoresis (see for example, page 16-17). For this additional reason, Schmidt fails to anticipate claim 43

In view of the foregoing discussion, the Applicants submit that Schmidt fails to anticipate claims 21-28, 31, 33-34, and 42-43 and respectfully request that the rejection of claims 21-31, 33-34 and 42-43 under 35 U.S.C. § 102(b) be withdrawn.

Claim Rejections under 35 U.S.C. § 103

Claims 29-30 and 32 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Schmidt et al. (WO 99/02728) in view of Singh (U.S. Patent No. 6,514,700). The Applicants respectfully traverse this rejection.

In order to meet its burden in establishing a rejection under 35 U.S.C. §103, the Office must first demonstrate that a prior art reference, or references when combined, teach or suggest all claim elements. *See, e.g., KSR Int'l Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 1740 (2007); *Pharmastem Therapeutics v. Viacell et al.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007); MPEP § 2143(A)(1). In addition to demonstrating that all the elements were known in the prior art, the Office must also articulate a reason for combining the elements. *See, e.g., KSR* at 1741; *Omegaflex, Inc. v. Parker-Hannifin Corp.*, 243 Fed. Appx. 592, 595-596 (Fed. Cir. 2007) (citing *KSR*). Further, the Supreme Court in *KSR* also stated that that "a court *must* ask whether the improvement is more than the predictable use of prior art elements

according to their established functions." *KSR* at 1740; emphasis added . As such, in addition to showing that all elements of a claim were known in the prior art and that one of skill had a reason to combine them, the Office must also provide evidence that the combination would be a predicted success.

The Examiner states that Schmidt is deficient in that Schmidt does not disclose that the cleavable tag is a fluorescent tag and it is acid or base cleavable. Singh is cited to meet Schmidt's deficiencies.

The Applicants submit that Schmidt is also deficient in that it fails to teach or suggest all the elements of the Applicants claims because, as noted above, Schmidt does not disclose, for example, cleaving said 3' cleavable tag from said extension product to produce a cleaved tag and an extension product that includes the at least one complementary nucleotide hybridized to or not separated from the template nucleic acid sequence, as required by the rejected claims.

Singh was cited solely for its alleged disclosure of a fluorescent tag and tags that are acid or base cleavable. Consequently, Singh fails to remedy the deficiencies of Schmidt. Therefore, the cited combination of Schmidt and Singh does not disclose or suggest all the elements of claims 29-30 and 32, and the Applicants respectfully request withdrawal of this rejection.

CONCLUSION

Applicant submits that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, please telephone James Keddie at (650) 327-3400.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-1078, order number 10010632-3.

Respectfully submitted,

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